The Malaysian Perspective on Biologics Regulation

Anis Talib
Deputy Director
Centre for Product Registration
National Pharmaceutical Control Bureau
Ministry of Health, Malaysia

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Talk Outline

• Regulatory overview of biologics in Malaysia
• Priorities in regulating biologics
• Malaysia’s participation in international regulatory convergence efforts
• Regulatory challenges:
  - Trends in biosimilar product development
  - Innovative approaches to accelerate development of critical medicines
Regulatory Overview at NPCB

Pre-marketing Authorisation

Centre for Investigational New Products

Centre for Compliance and Licensing

Centre for Quality Control

Centre for Product Registration

Biologics Product Registration Section

• Biotechnology Products
• Vaccines
• Blood- and Plasma-derived Products
• Cell and Gene Therapy Products

Marketing Authorisation

Post-marketing Authorisation

Centre for Post-registration of Products
No. of biological products registered in Malaysia (2010-2015):

<table>
<thead>
<tr>
<th>Product category</th>
<th>No. of registered products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibody (mAb)</td>
<td>22</td>
</tr>
<tr>
<td>Vaccine</td>
<td>21</td>
</tr>
<tr>
<td>Hormone/biological factor/cytokine</td>
<td>15</td>
</tr>
<tr>
<td>Blood/Plasma product</td>
<td>13</td>
</tr>
<tr>
<td>Human insulin &amp; analogues</td>
<td>7</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agent (ESA)</td>
<td>5</td>
</tr>
<tr>
<td>Antibody-drug conjugate (ADC)</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>85</td>
</tr>
</tbody>
</table>

No. of biological manufacturer in Malaysia: 1
Our Priorities ... 

Vision:
A nation working together for better health
Priority 1: Quality, Safety and Efficacy

- Biologics/Biosimilars are regulated as high risk medicinal products
- Malaysia National Medicine Policy (DUNas)
  - Restructuring of NPCB as an autonomous body
  - Enhancing regulatory capacity to ensure all regulatory requirements are on par with international standards, e.g:
    i. To be fully functional regulatory authority in biologics and vaccines (by 2017)
    ii. Nonclinical studies for new products to comply with OECD GLP
    iii. Publication of Cell and Gene Therapy Product Guidelines (Q1 2016)
- Effective enforcement, e.g. to ensure vaccines and blood product comply with cold chain requirements
- Pharmaceutical quality assurance through post-marketing surveillance (e.g: vaccines lot release, AEFIs) & management of product complaints
Priority 2: To maintain a high standard for biosimilars

- A direct and extensive comparability exercise with the reference product in terms of quality, safety and efficacy

- Distinguishable non-proprietary names for all biological medicines to enhance traceability

- Transparent information in biosimilar labels, to facilitate physician and patient understanding as well as respect for physicians’ prescribing authority

- Interchangeability and substitution - based on current science and clinical data

(Malaysia’s guidance document for registration biosimilars, 2008)
Priority 3:
Moving towards Made in Malaysia biologics

National Biotechnology Policy (NBP)

“Purpose is to create an integrated platform for participation by the scientific, business and funding groups to ensure an eco-system that is capable of sustaining Malaysia’s growth and progress in biotechnology.”
A Support Network that Extends Across Ministries

- **MIDA**: Attracting FDI to encourage growth
- **NPCB**: To facilitate speedy registration of biologic products (245 working days >>> 60 working days)
- **Biotechcorp**: Commercialising the discoveries of health-related natural products and biosimilars
- **Prime Ministers Department**: Conduit between public & private sectors
- **Tracking progress**

**Identified Entry Point Projects (EPPs)** in biosimilar & regenerative medicine

- Funding (RM100M, 2011-2015)
- Off-take agreement as economic incentive
The Proof is in the Pudding...

Iskandar rising

Iskandar Malaysia is rising as a vibrant and exciting growth corridor with huge investments in various sectors. The latest projects totalling about RM46bil in value are a motorsports city, nanotechnology industries, mixed development areas, a prime waterfront property, a trade centre, communication and ICT infrastructure, and a global innovation centre. > See Page 4

A nano technology-based industries centre in Nusajaya, expected to create more than RM1bil worth of business opportunities.

Nusajaya to be turned into one of the world’s leading interconnected smart communities, creating a seamless experience for residents, businesses and visitors.

Collaboration between UEM Land Bhd, Iskandar Investment Bhd, Telekom Malaysia Bhd, Centios Co Ltd and Cisco System International BV to establish a Global Innovation Centre for the Smart and Connected Nusajaya Master Plan.

A 109ha Motorsport City in Gerbang Nusajaya, including a 4.5km F1-compliant test track, car showrooms and other service centres. The venture, valued at over RM3.5bil is set to generate 5,000 jobs.

Sunway City Sdn Bhd and Iskandar Asset Sdn Bhd’s development of Sungai Pendas mixed development project similar to Bandar Sunway, with potential Gross Development Value (GDV) of RM12bil.

A China Mall, with a 12.9ha trade and exhibition centre in Gerbang Nusajaya, to cater to 3,000 traders from China and create 3,000 jobs for locals.

Prime 22.3ha waterfront land for mixed development project comprising hotels, condominiums, shopping malls, residential properties totalling RM18bil over the next 10 years.

Biocon

Biocon's Malaysia facility to be the largest integrated insulins facility of Asia
Biosimilar Insulin - Biocon (Insugen®)

- 1st biosimilar insulin approved in Malaysia
- Product previously registered via a non-biosimilar pathway in country of origin (India)
- Approved with conditions:
  - Implementation of Risk Management Plan, RMP
  - Pharmacovigilance
  - A registry of Insugen use in Malaysia
- Biocon Ltd’s biopharmaceutical manufacturing and R&D facility in Bio-Xcell, a biotech park and eco-system in Iskandar Malaysia
- In the first phase Biocon invested USD 161 million in insulin drug substance and drug product manufacturing facilities (target operation by 2016)
- The project also focuses on R&D and production of other products at a later phase
Benchmarking

- **Quality Management System:** Certified MS ISO 9001:2008
  Complimented by WHO during the WHO NRA Assessment System Audit and Institutional Development Plan (IDP) in 2013

- **Training centre for foreign regulatory authorities since 1986**
  - WHO Collaborating Centre for Regulatory Control of Pharmaceuticals
  - Regional Training Centre for ASEAN Technical Cooperation among Developing Countries (TCDC) Programme

- **Reference agencies:**
  - All biologics:
    - EMA (MHRA, Swedish Medicines Agency, ANSM France), US FDA, Health Canada, PMDA, Swissmedic, Australian TGA
  - Vaccines: WHO pre-qualified products

- **Current GMP for Quality Assurance of biologics:**
  PIC/S member authority since 2002

- **Non-OECD member adhering to Mutual Acceptance Data (MAD) since 2013**
  Principles of Good Laboratory Practice (GLP)
International Relations

- ACCSQ-PPWG:
  - ASEAN Common Technical Dossier (ACTD)
  - ICH climatic Zone IV stability testing requirements

- APEC Harmonization Center (AHC)’s regulatory convergence activities

- WHO:
  - Participant at the International Conference of Drug Regulatory Authorities (ICDRA)
  - Regular participation in guidelines formulation & implementation workshops
  - Joint technical consultation on evaluation of a novel dengue vaccine

*Rather than reinventing the wheel...*
Regulatory Challenges
### Evaluation of Biosimilars

Biosimilar products registered in Malaysia (2010-2015)

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Product brand name</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatropin</td>
<td>SciTropin</td>
<td>Sandoz</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Binocrit</td>
<td>Sandoz</td>
</tr>
<tr>
<td>Epoetin zeta</td>
<td>EPO STADA</td>
<td>Stada</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Zarzio</td>
<td>Sandoz</td>
</tr>
<tr>
<td></td>
<td>Nivestim</td>
<td>Hospira</td>
</tr>
<tr>
<td>Recombinant Human Insulin</td>
<td>Insugen</td>
<td>Biocon</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remsima</td>
<td>Celltrion</td>
</tr>
</tbody>
</table>
Evaluation of New Biosimilar Products - Regulatory Challenges

- Immunogenicity
  - Pure Red Cell Aplasia (PRCA) with EPO use
  - NPCB’s great foresight and persistence in an early establishment of a biosimilar registration pathway in 2008 avoided release of “me-too” and “bio-generic” products in Malaysia
  - On the other hand, Thailand registered 14 copy EPO products as generics. With detection of PRCA attributable to these non-biosimilar products, Thai FDA is re-assessing them via current biosimilar requirements [Praditpornsilpa K, et al., 2011]

- New monoclonal antibodies (mAbs)
  - Challenges in determining level of similarity and clinical study data required to establish comparability across all indications of the reference product
Evaluation of New Biosimilar Products
- Important Clinical Considerations

• Naming & labeling requirements
  • Is WHO’s INN for generics suitable for biosimilars?
  • Regulatory agencies establishing own naming conventions (US FDA, EMA, PMDA)

• Clinical use
  • Biosimilar and reference product interchangeability at prescriber level
  • Automatic substitution of reference product with biosimilar at pharmacy level
Evaluation of New Biosimilar Products - Legislative Challenges

Data exclusivity (DE)

- Subject to Malaysia signing the TPPA
- Test data protection for reference products
- During the DE period (~5-8 years post registration), regulatory authority will not be able to rely on innovator test data to grant market approval of biosimilars
Evaluation of New Biological Product Types

- Malaysia’s Bio-economy Transformation Programme (BTP) focuses on development of local biosimilars and Regenerative Medicine Products
- Trend at our reference regulatory agencies on innovative regulatory strategies for enabling the rapid development and the potential for early marketing approval of highly promising new biological products, e.g. Breakthrough Designation, Fast Track Approval
- In Malaysia, our **Priority Review** pathway allows for such flexibility in product registration. Product evaluation timeline is shortened from 245 working days to 90 working days.
- NPCB offers regulatory advice meetings (non-binding recommendations) to biological product developers (biosimilar, vaccine, Cell Therapy Products)

_Frequent interaction with product developers calls for continuous enhancement in regulatory capacity_
Moving forward

- NPCB endeavors to continue close working relations with benchmark regulatory agencies worldwide. “No regulatory agency is alone in facing the common regulatory challenges and building camaraderie among regulators will lighten everyone's burden”

- NPCB will continue to build its regulatory capacity by keeping up with cutting-edge bio-manufacturing methods to attain the nation’s vision of a local biologics industry

- NPCB strives to match appropriate regulatory control with biotechnological innovations to ensure adequate quality, efficacy, and safety of biologics